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09/819,249	03/27/2001	Scott A. Waldman	TJU-2412	2090

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EXAMINER	
SPIEGLER, ALEXANDER H	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/819,249	WALDMAN ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *1-24 (in part), 25-28 and 33-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 1-24 (in part) and 29-32) in Paper No. 11, filed on February 25, 2003 is acknowledged.

Applicants argue that a search for Groups I and II would not impose a serious burden, and therefore, the Groups should be examined together. Applicants' argument has been considered, but is not persuasive, since Groups I and II are directed to distinct types of cancer, stomach and esophageal cancer, respectively. Each cancer involves a different search and consideration. Furthermore, each of these methods has different modes of operation (e.g., assaying different types of individuals), different functions and effects (screening for stomach *or* esophageal cancer). Accordingly, the restriction requirement is made FINAL.

Claims 1-24 (in part), 25-28 and 33-38 are withdrawn from consideration, as being drawn to a non-elected invention.

Specification

2. Claims 1-24 are objected to because the claims are drawn to non-elected subject matter (e.g., stomach cancer). Applicants should amend the claims to include only the elected subject matter (e.g., methods of screening esophageal cancer).

Information Disclosure Statement

3. The information disclosure statements of Paper No. 5-8 and 12 comply with CFR 1.97, 1.98, and M.P.E.P. 609, and has been considered.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-24 and 29-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-24 and 29-32 over "GCC" because it is not clear as to exactly what a "GCC" encompasses. On page 4, the specification discusses "GCC":

> As used herein, the term "GCC" is meant to refer to ***the cellular protein expressed by normal colorectal cells, as well as primary and metastasized colorectal, stomach and esophageal cancer cells.*** In normal individuals, GCC is found exclusively in cells of intestine, in particular in cells in the duodenum, small intestine (jejunum and ileum), the large intestine, colon (cecum, ascending colon, transverse colon, descending colon and sigmoid colon) and rectum.

(Page 4, lines 24-29).

Therefore, GCC is defined as "the cellular protein" expressed by both normal and cancerous colorectal cells, and "the cellular protein" expressed by stomach and esophageal cancer cells. Given this definition, it is not clear as to what "cellular protein" is to be expressed, and therefore, it is not clear what constitutes or encompasses "GCC". Additionally, the specification discusses human GCC protein (pg. 5, ln. 6-8), and also states, "primary and metastatic stomach and esophageal cancer cells express ST receptors (GCC)". Therefore, it is also not clear as to whether human GCC protein is to be encompassed by "GCC" or "ST receptors" is to be encompassed by "GCC", etc.

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-24 and 29-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

35 U.S.C.§ 112, requires, *inter alia*, that a patent specification contain a written description of the invention and the manner and process of making and using it "...in such full clear and concise terms as to enable one skilled in the art... to make and use" the invention. While it is well settled that a patent application need not teach each possible embodiment of the claimed invention, it is manifestly true that written description cannot be settled by reliance on that which has not been achieved in the art, or that which is not disclosed in the specification. That is, a specification is not considered to satisfy the requirement for an adequate written description if it fails to disclose the specific starting materials or conditions for making the invention. (*Genentech, Inc. v. Novo Nordisk*, 108 F3d. 1361, 42 USPQ2d 100. Fed. Cir. 1997), or evidence that the applicants at the time the application was filed, has possession of the claimed invention.

Additionally, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention. The invention is, for purposes of the written [illegible] (See page 1117)." The specification does not

"clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed (See Vas-Cath at page 1116)."

Applicant's attention is also drawn to the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1st Paragraph, Written Description Requirement" (published in Federal Register/Vol. 66, No. 4/Friday, January 5, 2001/Notices; p. 1099-1111).

In the instant case, the claims are drawn to methods of screening an individual who is suspected of having primary and/or metastatic esophageal cancer comprising examining a sample of extraintestinal tissue and/or body fluids from an individual to determine whether GCC is being expressed by cells in said sample wherein expression of said GCC indicates a possibility of primary and/or metastatic esophageal cancer cells in said sample.

On page 4, the specification discusses "GCC":

> As used herein, the term "GCC" is meant to refer to ***the cellular protein expressed by normal colorectal cells, as well as primary and metastasized colorectal, stomach and esophageal cancer cells.*** In normal individuals, GCC is found exclusively in cells of intestine, in particular in cells in the duodenum, small intestine (jejunum and ileum), the large intestine, colon (cecum, ascending colon, transverse colon, descending colon and sigmoid colon) and rectum.

(Page 4, lines 24-29).

Therefore, "GCC" may encompass any "cellular protein" expressed by both normal and cancerous colorectal cells, and any "cellular protein" expressed by stomach and esophageal cancer cells. Given this description, the possible "cellular proteins" that could be reasonably interpreted by the recitation of "GCC" includes a large genus of possible proteins. Applicants have not described, contemplated, shown possession or any sufficient, relevant identifying characteristics, or experimented with any of these possible "cellular proteins". Additionally, the

specification gives no structural information as to what constitutes "GCC". Accordingly, there is not an adequate written description for the broadly claimed invention.

8. Claims 1-24 and 29-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. In *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

Also, MPEP 2164.01 states:

"Even though the statute does not use the term 'undue experimentation,' it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)."

The *Wands* court outlined several factors to be considered in determining whether a disclosure would require undue experimentation:

"They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.* at 1404.

In the instant case, the specification does not enable one of skill in the art to make and use the claimed invention for the following reasons:

(1) The quantity of experimentation necessary

In order to practice the invention, the practitioner must determine what cellular protein is expressed by normal colorectal cells, as well as, primary and metastasized colorectal, stomach and esophageal cancer cells (i.e., the skilled artisan must determine what proteins can be considered "GCC"). This process is not only difficult, but unpredictable, since the specification does not teach any structural or functional guidelines as to what cellular proteins are expressed by normal colorectal cells, as well as, primary and metastasized colorectal, stomach and esophageal cancer cells. In other words, since it is not clear as to what constitutes "GCC" the skilled artisan would not know how to carry out the claimed invention.

Even assuming the practitioner determines what cellular protein satisfies the specification's description of "GCC" (see 112, 1st and 2nd paragraph rejections above for discussion of specification's definition of "GCC"), he must then experiment to determine whether expression of "GCC" is correlated with esophageal cancer. This experiment, at least,

esophageal cancer. Additionally, the skilled artisan will have to determine if an increased or decreased expression is diagnostic for esophageal cancer.

In essence, the experimentation that one skilled in the art would be required to perform is in fact the proposed novelty of the invention. "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement." (*Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001).

Therefore, the quantity of experimentation is not only difficult, but also unpredictable.

(2) The amount of direction or guidance presented

The specification provides guidance on general methods of how to measure expression of esophageal tumors (pgs. 12-32), but does not provide any guidance as to what is encompassed by "GCC", and therefore, the specification does not provide guidance on the claimed methods.

(3) The presence or absence of working examples

No working examples are present that show the correlation between "GCC" and esophageal cancer. The specification states only a conclusion, "in addition to normal colon cell, to primary and to metastasized colon, stomach and esophageal carcinoma cells also express GCC. Normal stomach and esophageal cells do not express GCC." (pg. 11, lines 15-17)

(4) The nature of the invention

The invention is directed to methods of screening an individual who is suspected of having primary and or metastatic esophageal cancer comprising examining a sample of extraintestinal tissue and/or body fluids from an individual to determine whether GCC is being expressed by cells in said sample wherein expression of said GCC indicates a possibility of

primary and/or metastatic esophageal cancer cells in said sample. Thus, the nature of the invention pertains to genetic screening for detection/diagnosis of disease.

(5) The state of the prior art

The prior art of Carrithers et al. (PNAS (1996) 93:14827-32, cited in the IDS) teaches that Guanylyl cyclase C is not expressed in normal esophagus tissue (pg. 14829, Fig. 1). Iannettoni et al. (Ann Thorac Surg. (1996) 62:1460-6, cited in the IDS) and Wu et al. (Gastroenterology (1993) 105:837-844, cited in the IDS) teach that the expression of sucrase-isomaltase is diagnostic of esophageal cancer.

(6) The relative skill of those in the art

The level of skill in molecular biology is high, as one of ordinary skill in the art would have to experiment and determine what cellular protein is expressed by normal colorectal cells, as well as, primary and metastasized colorectal, stomach and esophageal cancer cells. Not only would this endeavor be time consuming, but also it would be very unpredictable, as there is no guidance from the specification as to what cellular proteins fit the definition of "GCC", let alone be used to screen for the predisposition of esophageal cancer.

(7) The predictability or unpredictability of the art

The correlation between specific genes and the diagnosis for the predisposition to esophageal cancer by expression analysis of "GCC" is very unpredictable as summarized above.

(8) The breadth of the claims

The invention is directed to methods of screening an individual who is suspected of having primary and or metastatic esophageal cancer comprising examining a sample of

protein is expressed by normal colorectal cells, as well as, primary and metastasized colorectal, stomach and esophageal cancer cells, is being expressed by cells in said sample wherein expression of said cellular proteins indicates a possibility of primary and/or metastatic esophageal cancer cells in said sample.

Accordingly, in view of the unpredictability in the art and in view of the lack of specific disclosure in the specification, undue experimentation would be required to practice the invention as it is claimed.

Applicants are reminded that the enablement requirement of 35 U.S.C. 112, first paragraph, is separate and distinct from the description requirement. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116-17 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-6, 9-16, 19-24 and 29-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Iannettoni et al. (Ann Thorac Surg. (1996) 62:1460-6, cited in the IDS), or Wu et al. (Gastroenterology (1993) 105:837-844, cited in the IDS).

Given the lack of description and clarity of the recitation of "GCC" (see above 112 rejections), the claims have been interpreted as encompassing using any expression that is diagnostic of esophageal cancer.

Iannettoni and Wu et al. both teach the expression of sucrase-isomaltase is diagnostic of esophageal cancer. For example, Iannettoni teaches the RNA isolation of tissue samples, RT-PCR followed by immunohistochemistry to determine expression in normal esophagus vs. expression in Barrett's esophagus and esophageal adenocarcinoma (see pages 837-840, for example).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-6, 9-16 and 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carrithers et al. (PNAS (1996) 93:14827-32, cited in the IDS).

The claims are drawn to screening an individual for the "possibility" or that an individual "may have" primary and/or metastatic esophageal cancer cells by determining whether "GCC" is expressed.

Carrithers teaches that Guanylyl cyclase C ("GCC") is not expressed in normal esophagus tissue (pg. 14829, Fig. 1). Because "GCC" is not expressed in normal esophagus tissue there is a "possibility" that an individual "may have" primary and or metastatic esophageal cancer cells. Carrithers does not teach using "GCC" expression in esophageal tissues as a diagnostic for esophageal cancer cells.

[illegible] would have been obvious to one of

expression in normal esophageal tissue would elicit the "possibility" that an individual who does express "GCC" "may have" primary and/or metastatic esophageal cancer cells, therefore, using "GCC" expression as a diagnostic for primary and/or metastatic esophageal cancer cells.

Conclusion

13. No claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014. Applicant is also invited to contact the TC 1600 Customer Service Hotline at (703) 308-0198.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
May 27, 2003

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
5/27/03